Amendments to the Specification:

Please replace the paragraph on page 1, lines 34-41, with the following amended paragraph:

Physiological changes in anaphylactic hypersensitivity can include intense constriction of the bronchioles and bronchi of the lungs, contraction of smooth muscle and dilation of capillaries. Predisposition to this condition, however, appears to result from an interaction between genetic and environmental factors. Common environmental allergens which induce anaphylactic hypersensitivity are found in pollen, foods, house dust mites, animal danders, fungal spores and insect venoms. Atopic allergy is associated with anaphylactic hypersensitivity and includes the disorders, e.g., asthma, allergic rhinitis and conjunctivitis (hay fever), eczema, urticaria and food allergies. However anaphylactic ~~shoebk~~shock, a dangerous life-threatening condition anaphylaxis is usually provoked by insect stings or parental medication.

Please replace the paragraph on page 7, lines 2-13 with the following amended paragraph:

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of the environment in which ~~is~~it was produced. Contaminant components of its production environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified as measurable by at least three different methods: 1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight; 2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup ~~sequentator~~sequenator; or 3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomasie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the

antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

Please replace the paragraphs beginning on page 7, lines 23 and ending on page 8, line 5 with the following amended paragraph:

The term "antibody mutant" refers to an amino acid sequence variant of an antibody wherein one or more of the amino acid residues have been modified. Such ~~mutant~~mutants necessarily have less than 100% sequence identity or similarity with the amino acid sequence having at least 75% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the antibody, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%. Since the method of the invention applies equally to both polypeptides, antibodies and fragments thereof, these terms are sometimes employed interchangeably.

The term "variable" in the context of variable domain of antibodies, refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed through the variable domains of antibodies. It is concentrated in three segments called complementarity determining regions (CDRs) also known as hypervariable regions both in the light chain and the heavy chain variable domains. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al., Sequences of Proteins of Immunological Interest (National Institute of Health, Bethesda, MD 1987); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Chothia, C. et al. (1989), Nature 342: 877). With respect to Applicants' anti-IgE antibody, certain CDRs were defined by combining the Kabat et al. and Chothia et al. approaches. The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-sheet configuration, connected by three

CDRs, which form loops connecting, and in some cases forming part of, the β-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies (see Kabat et al.). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector function, such as participation of the antibody in antibody-dependent cellular toxicity.

Please replace the paragraph at page 10, lines 34-35 with the following amended paragraph:

"Transformation" means introducing DNA into an organism so that the DNA is replicable, either as an extrachromosomal element or by chromosomal integration.

Please replace the paragraph at page 12, lines 13-33 with the following amended paragraph:

The term "immunosuppressive agent" as used herein for adjunct therapy refers to substances that act to suppress or mask the immune system of the host into which a graft is being transplanted. This would include substances that suppress cytokine production, downregulate or suppress self-antigen expression, or mask the MHC antigens. Examples of such agents include 2-amino-5-aryl-5-substituted pyrimidines (See U.S.P. 4,665,077), azathioprine (or cyclophosphamide, in case of adverse reaction to azathioprine); bromocryptine; glutaraldehyde (which masks the MHC antigens, as described in U.S. Pat. No. 4,120,649); anti-idiotypic antibodies for MHC antigens and NHC fragments; cyclosporin A; steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisone, and dexamethasone; cytokine or cytokine receptor antagonists including anti-interferon-γ, -β, or α-antibodies; anti-tumor necrosis factor-α antibodies; anti-tumor necrosis factor-β antibodies; anti-interleukin-2 antibodies and anti-IL-2 receptor antibodies; anti-L3T4 antibodies; heterologous anti-lymphocyte globulin; pan-T antibodies, preferably anti-CD3 or anti-CD4/CD4a antibodies; soluble peptide containing a LFA-3 binding domain (WO 90/08187 published July 26 1990); streptokinase; TGF-β;

streptodornase; RNA or DNA from the host; FK506; RS-61443; deoxyspergualin; rapamycin; T-cell receptor (U.S.P. 5,114,721); T-cell receptor fragments (Offner *et al., Science* 251: 430-432 (1991); WO 90/11294; and WO 91/01133); and T cell receptor antibodies (EP 340,109) such as T10B9. These agents are administered at the same time or at separate times from CD11a antibody, and are used at the same or lesser dosages than as set forth in the art. The preferred adjunct immunosuppressive agent will depend on many factors, including the type of disorder being treated including the type of transplantation being performed, as well as the patient's history, but a general overall preference is that the agent be selected from cyclosporin A, a glucocorticosteroid (most preferably prednisone or methylprednisolone), OKT-3 monoclonal antibody, azathioprine, bromocryptine, heterologous anti-lymphocyte globulin, or a mixture thereof.

Please replace the paragraph at page 15, lines 1-3 with the following amended paragraph:

Alternatively, the method includes polypeptides which are composed of more than one subunit, wherein the ~~the~~ replicable expression vector comprising a transcription regulatory element operably linked to DNA encoding the subunit of interest is fused to the phage coat protein.

Please replace the paragraph at page 16, lines 18-23 with the following amended paragraph:

Preferably during the affinity maturation process, the replicable expression vector is under tight control of the transcription regulatory element, and the culturing conditions are adjusted so that the amount or number of phagemid particles displaying more than one copy of the fusion protein on the surface of the particle is less than about 1%. Also preferably, the amount of phagemide particles displaying more than one copy of the fusion protein is less than 10% the amount of phagemid ~~eparticles~~particles displaying a single copy of the fusion protein. Most preferably the amount is less than 20%.

Please replace the paragraph beginning at page 16, line 28 and ending at p 17, line 4 with the following amended paragraph:

Also typically, the first gene will encode a mammalian protein, preferably, the protein will be an anti-IgE antibody. Additional antibodies are exemplified in section II.A. Antibody preparation, (vi) *multispecific antibodies* (note however, that antibodies need not be multispecific). Additional polypeptides include human growth hormone (hGH), N-methionyl human growth hormone, bovine growth hormone, parathyroid hormone, thyroxine, insulin A-chain, insulin B-chain, proinsulin, relaxin A-chain, relaxin B-chain, prorelaxin, glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (THS), and leutinizing hormone (LH), glycoprotein hormone receptors, calcitonin, glucagon, factor VIII, lung surfactant, urokinase, streptokinase, human tissue-type plasminogen activator (t-PA), bombesin, factor IX, thrombin, hemopoietic growth factor, tumor necrosis factor-alpha and -beta, enkephalinase, human serum albumin, mullerian-inhibiting substance, mouse gonadotropin-associated peptide, a microbial protein, such as betalactamase, tissue factor protein, inhibin, activin, vascular endothelial growth factor, receptors for hormones or growth factors, integrin, thrombopoietin, protein A or D, rheumatoid factors, nerve growth factors such as NGF-β, platelet-growth factor, transforming growth factors (TGF) such as TGF-alpha and TGF-beta, insulin-like growth factor-I and -II, insulin-like growth factor binding proteins, CD-4, DNase, latency associated peptide, erythropoietin, osteoinductive factors, interferons such as interferon-alpha, -beta and -gamma, colony stimulating factors (CSFs) such as M-CSF, GM-CSF and G-CSF, interleukins (~~Hs~~ILs) such as IL-1, IL-2, IL-3, IL-4, superoxide dismutase, decay accelerating factor, viral antigen, HIV envelope proteins such as GP120, GP140, atrial natriuretic peptides A, B or C, immunoglobulins, and fragments of any of the above-listed proteins.

Please replace the paragraph at page 25, lines 5-13 with the following amended paragraph:

In constructing a replicable expression vector containing DNA encoding the protein of interest having multiple subunits, the reader is referred to ~~Figure 11~~Figures 11A and B, where,

by way of illustration, a vector is diagramed showing DNA encoding each subunit of an antibody fragment. This figure shows that, generally, one of the subunits of the protein of interest will be fused to a phage coat protein such as M13 gene III. This gene fusion generally will contain its own signal sequence. A separate gene encodes the other subunit or subunits, and it is apparent that each subunit generally has its own signal sequence. ~~Figure 11~~Figures 11A and 11B also ~~shows~~show that a single promoter can regulate the expression of both subunits. Alternatively, each subunit may be independently regulated by a different promoter. The protein of interest subunit-phage coat protein fusion construct can be made as described in Section IV above.

Please replace the paragraph at page 30, lines 17-18 with the following amended paragraph:

Monoclonal antibodies may be made ~~musing~~using the hybridoma method first described by Kohler *et al.*, *Nature*, 256: 495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

Please replace the paragraph beginning at page 37, line 24 and ending page 38, line 3 with the following amended paragraph:

The antibody mutant(s) so selected may be subjected to further modifications, oftentimes depending upon the intended use of the antibody. Such modifications may involve further alteration of the amino acid sequence, fusion to heterologous polypeptide(s) and/or covalent modifications such as those elaborated below. With respect to amino acid sequence alterations, exemplary modifications are elaborated above. For example, any ~~cysteines~~cysteine residues not involved in maintaining the proper conformation of the antibody mutant also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant cross linking. Conversely, (a) cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment). Another type of amino acid mutant has an altered glycosylation pattern. This may be achieved by deleting one or more carbohydrate moieties found in the antibody, and/or adding one or more

glycosylation sites that are not present in the antibody. Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of a sugar through an ether oxygen; For example, N-acetylgalactosamine, galactose, fucose or xylose bonded to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used. Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

Please replace the paragraph at page 40, lines 4-12 with the following amended paragraph:

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al.*, *Science* 229: 81 (1985) describes a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vincinal dithiols and prevent intermolecular disulfide formation. The F(ab') fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Please replace the paragraph at page 41, lines 35-41 with the following amended paragraph:

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al., J. Biol. Chem.* 257: 286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al., J. National Cancer Inst.* 81(19): 1484 (1989).

Please replace the paragraph at page 55, lines 11-20 with the following amended paragraph:

In another embodiment of the invention, an article of manufacture containing materials useful for the treatment of the disorders described above is provided. The article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the antibody mutant. The label on, or associated with, the container indicates that the composition is used for treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

Please replace the paragraph at page 60, lines 1-3, with the following amended paragraph:

d. The cells were then incubated in 100 µl FACS buffer containing FITC conjugated F(ab')$_2$ goat anti-mouse IgG at 50 µg/ml (Organon Teknika, #1711-0084) for 30 minutes at 4°C followed by 3 washes with FACS buffer.

Please replace the paragraph at page 64, lines 5-8 with the following amended paragraph:

To test the effects of buried residues on CDR conformation, F(ab)-3 to F(ab)-7 were constructed in which murine residues were changed back to human ones. As is indicated in Table 4 (by F(ab)-3 & F(ab)-4), the side chains at VL4 and VL33 have minimal effect on binding and ~~presumeably~~presumably the conformation of CDR-L1 in the humanized antibody.

Please replace the paragraph at page 74, lines 12-21 with the following amended paragraph:

To evaluate the relative IgE binding affinities, phage were titrated on a plate coated with IgE as described above to normalize the displayed F(ab) concentrations. Phage were pre-mixed with serial dilutions of IgE, then added to an IgE-coated plate, and incubated for 1 hour at room temperature. The plates were then washed ten times with PBS/Tween, and a solution of rabbit anti-phage antibody mixed with a goat-anti-rabbit conjugate of horseradish peroxidase was added. After 1 hour incubation at room temperature, the plates were developed with a chromogenic substrate, o-phenylenediamine (Sigma). The reaction was stopped with addition of 1/2 volume of 2.5 M H_2SO_4. Optical density at 490 nm was measured on a spectrophotometric plate reader. The IC50 of each variant was determined by fitting a 4-parameter curve to each data set (Lowman, *Methods in Mol. Biol.*, *supra*). The relative binding affinity of each cloned phage variant was determined as the ratio of its IC50 to that of the starting phage, e426 (Tables 15-16).